Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 33, No. 6, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00081-9

Prognostic Significance of Elevated Hemostatic Markers in Patients With Acute Myocardial Infarction

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OBJECTIVES The purpose of this study was to determine whether the elevated levels of hemostatic markers in the early phase of myocardial infarction may serve as risk factors for subsequent cardiac mortality.

BACKGROUND Increased plasma hemostatic markers were noted in acute myocardial infarction, indicating that the blood coagulation system is highly activated in those patients. However, there are few clinical data concerning the association between the elevated hemostatic markers and survival in patients with myocardial infarction.

METHODS Blood samples were obtained from 64 patients (mean age 67 ± 11 years; 49 male) with acute myocardial infarction within 12 h after the onset of symptoms and before the initiation of any antithrombotic treatment. We measured plasma concentrations of fibrinopeptide A (FPA), prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin complex (TAT) using the enzyme-linked immunosorbent assay method, and examined the associations between the level of these markers and survival with Cox proportional hazards models.

RESULTS The follow-up time was 27 ± 17 months, and 19 patients died of cardiac causes during the follow-up. Univariate survival analysis identified Killip class IV (hazard ratio 4.86; 95% confidence interval [CI] 1.55–15.19), left ventricular ejection fraction (hazard ratio 0.94; 95% CI 0.90–0.99), FPA (hazard ratio 1.54; 95% CI 1.13–2.10), F1+2 (hazard ratio 2.03; 95% CI 1.17–3.53) and TAT (hazard ratio 1.88; 95% CI 1.27–2.79) as significant factors associated with cardiac mortality. In multivariate analyses, only FPA level (hazard ratio 1.84; 95% CI 1.03–3.30) and left ventricular ejection fraction (hazard ratio 0.93; 95% CI 0.88–0.98) were independent predictors of cardiac mortality.

CONCLUSIONS Elevated FPA in the early phase of myocardial infarction identifies patients with increased risk for subsequent cardiac death. This association appears to be independent of residual left ventricular function after infarction. (J Am Coll Cardiol 1999;33:1543–8) © 1999 by the American College of Cardiology

Intracoronary thrombus formation is the most important pathogenetic mechanism in unstable angina and acute myocardial infarction (1–4). The thrombi can be demonstrated clearly by angiographic (5,6), angioscopic (7,8) and histological examinations (9,10) in coronary arteries of these patients. Thrombotic process involves a chain of reactions that transform, in sequence, a number of coagulation factors present as precursors in plasma into an activated form, and lead to thrombin generation with subsequent fibrin and clot formation. Several highly sensitive and specific hemostatic markers have been developed that can monitor the activities of coagulation system in vivo. The most extensively studied hemostatic markers are fibrinopeptide A (FPA) (11,12) and prothrombin fragment 1+2 (F1+2) (13,14). FPA is the polypeptide cleaved from fibrinogen by thrombin, and hence a sensitive marker of thrombin activity and early fibrin formation. F1+2 is released from the amino-terminal end of prothrombin during thrombin generation and it indicates the activity of factor Xa. Many studies have demonstrated that coagulation system is highly activated in the acute phase of unstable angina and myocardial infarction (15–17). The plasma levels of FPA and F1+2 were significantly elevated in patients with acute coronary syndromes when compared with those with stable angina (15–17). Thrombin is neutralized by its physiological inhibitor anti-

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This work was presented in part at the 47th Annual Scientific Session of the American College of Cardiology, Atlanta, Georgia, March 1998.

Manuscript received July 6, 1998; revised manuscript received October 15, 1998, accepted January 21, 1999.

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Abbreviations and Acronyms
FPA = fibrinopeptide A
F1+2 = prothrombin fragment 1+2
TAT = thrombin-antithrombin complex

thrombin III. The thrombin-antithrombin complex (TAT) is another important procoagulant marker. It was also found to be increased in patients with acute myocardial infarction (18). Although coagulation activation with thrombosis formation is important in the pathogenesis of acute coronary syndromes, there are few studies concerning the influence of hemostatic function on clinical outcomes in these patients. Previous studies showed that increased plasma FPA could predict in-hospital adverse cardiac events after the attack of unstable angina or myocardial infarction (18,19). However, it is unknown whether these hemostatic markers may predict the long-term outcome in patients with acute coronary syndromes. Therefore, in this study, we measured the plasma hemostatic markers in patients suffering from acute myocardial infarction and evaluated their usefulness in predicting the survival of these patients.

METHODS

Study population. Seventy consecutive patients admitted to the National Cheng Kung University Hospital with the diagnosis of acute myocardial infarction from January 1993 to March 1994 were included in this study. Among them, six were excluded because we were unable to obtain current information regarding these patients. The remaining 64 patients (mean age 67 years; range 29 to 88 years) form the basis of this study. The diagnosis of acute myocardial infarction was based on a history of prolonged ischemic chest pain, characteristic electrocardiographic changes and elevation of cardiac enzymes. Blood samples for hemostatic markers measurement (FPA, F1+2, TAT) were obtained immediately from these patients in the emergency room or coronary care unit within 12 h after the onset of symptoms and before the initiation of any thrombolytic or anticoagulant treatment. After admission, all patients received regular medical treatment for myocardial infarction, including angiotensin converting enzyme inhibitor or beta-adrenergic blocking agent as indicated, and 53 of them received intravenous thrombolytic therapy. Revascularization procedures were performed on 16 patients either by percutaneous transluminal coronary angioplasty (n = 13) or coronary graft bypass surgery (n = 3) at a mean time of 12 days after the onset of myocardial infarction. According to the electrocardiographic criteria, the site of infarction was anterior in 37 patients, inferior in 25 patients and at other locations in 2 patients. Killip classification (20) based on physical findings during admission was determined in each patient as a prognostic guide. The left ventricular ejection fraction was measured using the Teichholz formula (21) from transthoracic echocardiography. No patient had a previous drug history of warfarin. There were also no histories of hemostatic disorders, malignancies or chronic inflammatory diseases in these patients. The mean follow-up period was 27 ± 17 months, ranging from 1 day to 53 months. The survival of each patient was assessed either to the day of death or to July 31, 1997. Follow-up data of these patients were obtained from detailed chart review and contact with patients or their families if necessary. The study protocol was approved by the Institutional Research Committee of our hospital.

Sample preparation. Blood samples were collected with the two-syringe technique by clean, flawless venipuncture using a 20-gauge needle. After the first 3 mL was discarded, the blood for FPA measurement was collected in a tube with special anticoagulant solution containing citrate, heparin and specific protease inhibitor. The ratio of anticoagulant to blood was 1:9 (vol/vol). All samples were stored in ice and immediately centrifuged at 4°C for 10 min at 1,500 *g*. The supernatant plasma was collected and treated with bentonite to remove fibrinogen, and then the plasma was frozen at −70°C until use. FPA was measured by commercial enzyme-linked immunoassay kits (Diagnostica Stago, Asnieres sur Seine, France) within one month after collection. The value was expressed as ng/mL. For F1+2 and TAT measurement, 9 mL venous blood was mixed carefully with 1 mL sodium citrate solution (0.11 mol/liter). The samples were immediately centrifuged at 4°C for 10 min at 1,500 *g*. The supernatant plasma was collected and immediately frozen at −70°C until use. Commercial enzyme-linked immunoassay kits (Diagnostica Stago, France) were used to measure F1+2. TAT was also measured by similar commercial enzyme-linked immunoassay kits (Behringwerke, Marburg, Germany). The values were expressed as nmol/L for F1+2 and ng/mL for TAT. The normal ranges of these hemostatic markers in our laboratory from 16 healthy control subjects matched for age and sex with the cardiac patients were: 4.3 ± 0.3 ng/mL for FPA, 0.9 ± 0.1 nmol/liter for F1+2 and 1.5 ± 0.3 ng/mL for TAT.

Statistical analysis. The clinical characteristics and levels of hemostatic markers were compared between patients with and without cardiac mortality. In comparing clinical characteristics between the groups, the chi-square test was used to evaluate the differences in categoric variables, and the Student *t* test was used to test the differences in continuous variables. As plasma levels of hemostatic markers were nonnormally distributed, the Wilcoxon rank sum test was used to evaluate the differences in these variables. The Pearson correlation analysis was used to assess the relations of plasma level of each hemostatic marker with patient's age, maximal creatine kinase and left ventricular ejection fraction. Survival analyses were conducted using the Cox proportional hazards models. Univariate analysis was used to examine correlations between clinical characteristics

(age, gender, hypertension, diabetes, smoking, cholesterol, previous infarction, Killip classification, thrombolytic therapy, revascularization procedure and maximal creatine kinase level) as well as hemostatic markers and survival after myocardial infarction. The data for hemostatic markers were analyzed in a logarithmic scale to reduce the skew in the data. Multivariate Cox proportional hazards models were used to assess the relation between hemostatic markers and other clinical variables. Each hemostatic marker was evaluated in a model that included the clinical characteristics that appeared to be statistically significant predictors of survival. Survival curves were constructed according to the method of Kaplan and Meier (22). In constructing the curves, each hemostatic marker was dichotomized to provide approximately equal numbers of deaths in the two comparison groups. All data were expressed as mean ± SE. A p value <0.05 was considered statistically significant. The statistical analyses were carried out using SAS for Windows Version 6.11.

RESULTS

During the follow-up period, 19 patients died due to cardiac causes, and 45 patients were alive at the end of this study. Seven patients died of sudden cardiac death, five patients died of cardiogenic shock, five patients died of refractory heart failure and two patients died of cardiac free-wall rupture. The clinical characteristics, follow-up periods and causes of death are shown in Table 1. These patients died from 1 day to 25 months after onset of acute myocardial infarction. The cardiac mortality was spread evenly over the duration of follow-up and was not found to be concentrated shortly after myocardial infarction. Table 2 shows the baseline clinical characteristics and hemostatic markers in patients with or without cardiac mortality. There were no significant differences in the coronary risk factors, sites of infarction, previous infarctions and modalities of treatment (thrombolytic therapy or revascularization procedures) between the patients who survived and died. The patients who died subsequently due to cardiovascular causes had higher percentages of Killip class IV and lower left ventricular ejection fractions. The initial levels of the three hemostatic markers (FPA, F1+2 and TAT) were also significantly higher in these patients. When patients were grouped according to the site of infarction, we found no statistically significant differences of hemostatic marker level in FPA (8.1 ± 2.1 vs. 7.2 ± 2.4; p = NS), F1+2 (4.0 ± 0.7 vs. 5.4 ± 0.9; p = NS) or TAT (13.9 ± 3.5 vs. 19.3 ± 4.4; p = NS) between those with anterior and inferior myocardial infarction. There were also no significant correlations of plasma FPA, F1+2 or TAT with patient's age (r = 0.17, −0.01, −0.10), maximal creatine kinase (r = −0.09, 0.02, 0.02) and left ventricular ejection fraction (r = 0.13, 0.05, −0.09; all p = NS).

Table 3 summarizes the associations of clinical characteristics and hemostatic markers with survival after myocardial infarction. Using univariate Cox proportional hazards models, we found that Killip class IV, left ventricular ejection fraction and logs of each of the three hemostatic markers were significantly associated with patient mortality (Table 3). The influence of elevated hemostatic markers on survival is illustrated in Figure 1. In Kaplan-Meier survival analyses, the hemostatic marker levels were dichotomized to provide an approximately equal number of deaths in the two groups. The groups with elevated hemostatic markers on admission showed significantly higher mortality rates (Fig. 1). Furthermore, according to multivariate Cox proportional hazards models, log (FPA) level (hazard ratio 1.84; 95% confidence interval [CI] 1.03–3.30; p = 0.04) and left ventricular ejection fraction (hazard ratio 0.93; 95% CI 0.88−0.98; p = 0.006) were the only independent predictors of cardiac mortality. This indicates that the initial FPA level may provide prognostic significance independent of usual clinical characteristics including left ventricular function after myocardial infarction.

Table 1. Clinical Characteristics, Follow-up Periods and Causes of Death in Patients With Cardiac Mortality

Age (yr) Gender	Infarction Site	Peak CK (U/L)	Follow-up Period	Cause of Death
75/M	inferior	2390	1 d	cardiogenic shock
62/F	anterior	1551	2 d	sudden cardiac death
56/F	anterior	1342	3 d	cardiogenic shock
66/M	inferior	3224	4 d	cardiogenic shock
69/M	inferior	3084	4 d	cardiac rupture
69/M	anterior	913	10 d	cardiogenic shock
85/M	anterior	1683	13 d	refractory CHF
75/F	anterior	2360	1 mo	reinfarction with cardiac rupture
68/M	inferior	3141	1 mo	sudden cardiac death with VF
52/M	anterior	2576	1 mo	refractory CHF
61/M	inferior	2957	3 mo	angina with VF
74/F	anterior	1639	4 mo	sudden cardiac death with VF
73/M	anterior	4454	4 mo	refractory CHF
76/F	inferior	3437	12 mo	sudden cardiac death
74/M	inferior	3430	14 mo	reinfarction with cardiogenic shock
71/M	anterior	2915	17 mo	refractory CHF
79/F	anterior	668	20 mo	sudden cardiac death
81/M	inferior	1906	22 mo	reinfarction with CHF
64/F	inferior	5365	25 mo	sudden cardiac death

CHF = congestive heart failure; VF = ventricular fibrillation.

DISCUSSION

Several recent studies have shown that elevated plasma levels of hemostatic markers are associated with increased risk of early adverse cardiac events in patients with acute coronary syndromes (18,19). In current study, we found that the initial plasma levels of FPA, F1+2 and TAT are good

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Table 2. Comparison of Clinical Characteristics and Hemostatic Markers Between Patients With and Without Cardiac Death

	Cardiac Death		
	No (n = 45)	Yes (n = 19)	p Value
Clinical characteristics:			
Age (yrs)	65.7 ± 1.8	70.0 ± 1.9	NS
Male	37 (82%)	12 (63%)	NS
Hypertension	23 (51%)	12 (63%)	NS
Diabetes	9 (20%)	5 (26%)	NS
Smoking	36 (80%)	11 (58%)	NS
Cholesterol (mg/dl)	195.6 ± 7.0	183.9 ± 11.5	NS
Thrombolytic therapy	39 (87%)	14 (74%)	NS
Revascularization	14 (31%)	2 (11%)	NS
Anterior MI	27 (60%)	10 (53%)	NS
Previous MI	7 (16%)	2 (11%)	NS
Maximal CK (U/liter)	2581.8 ± 313.7	2,593.1 ± 286.8	NS
Medication	28 (62%)	8 (42%)	NS
Killip class IV	2 (4%)	6 (32%)	< 0.01
Left ventricular EF (%)	55.4 ± 2.3	42.2 ± 3.2	< 0.01
Hemostatic markers:			
FPA (ng/ml)	3.9 ± 1.2	13.1 ± 3.1	< 0.01
F1+2 (nmol/liter)	3.7 ± 0.5	6.7 ± 1.2	< 0.01
TAT (ng/ml)	11.2 ± 2.6	27.3 ± 5.7	< 0.01

CK = creatine kinase; EF = ejection fraction; FPA = fibrinopeptide A; F1+2 = prothrombin fragment 1+2; Medication = Beta blocker or angiotensin-converting enzyme inhibitor; MI = myocardial infarction; TAT = thrombin-antithrombin complex. Data are presented as mean ± SE or number (%) of patients with the condition.

predictors of mortality not only in the acute phase of myocardial infarction but also in the long-term outcome. Moreover, the correlation between FPA and survival after myocardial infarction is independent of the residual left ventricular function. Thus, FPA appears to provide additional information on prognosis after myocardial infarction.

Prognostic value of hemostatic marker. Ardissino et al. (19) first demonstrated that patients with increased levels of FPA had a significantly higher probability to develop cardiac events during hospitalization. The independent variables predicting early unfavorable outcome in these patients were the presence of persistent ischemia on 24-h Holter monitoring, the presence of intracoronary thrombosis at angiography and abnormal plasma FPA level. The results of this study clearly demonstrated the close association between the activation of coagulation and adverse clinical outcome. Recently, the data from the Thrombolysis in Myocardial Infarction (TIMI)-5 Study (18) also suggest that hemostatic markers may be useful in predicting short-term clinical outcome in patients with acute myocardial infarction treated with thrombolytic therapy. They found that increased levels of FPA and TAT at 1 h after thrombolytic therapy were associated with higher in-hospital mortality. In our study, increased levels of hemostatic markers, especially FPA, in the acute phase of myocardial infarction were strongly associated with subsequent cardiovascular mortality. The cardiac death was spread evenly over the duration of follow-up and not concentrated shortly after myocardial infarction. Our study is the first one to suggest that elevated hemostatic markers in the early stage of myocardial infarction not only links to immediate death during hospitalization but also predicts a poor long-term prognosis in these patients. The correlation between FPA and survival was also independent of residual left ventricular systolic function after myocardial infarction. Our data may have important clinical potential because plasma level of FPA is easily measured in clinical laboratories, and this noninvasive marker may provide additional prognostic information regarding subsequent risk of death in acute myocardial infarction patients.

Mechanisms of hemostatic markers as prognostic indicators. It is still uncertain about the definite underlying mechanisms for the association between elevated hemostatic markers and adverse clinical outcome in acute coronary syndromes. The increased coagulation activation markers in these patients reflect an active intracoronary thrombotic process. Wilensky et al. (23) used angiographic features to grade the probability of intracoronary thrombus formation from 0 (no thrombus) to 4 (definite thrombus) in patients with unstable angina. They found that FPA levels correlated significantly with the presence of grade 3 or 4 intracoronary thrombus. Thrombosis formation in coronary arteries results from the rupture or fissuring of atherosclerotic plaques and exposure of procoagulant subendothelial surface to blood. However, the factors that determine the thrombus burden have not been well defined. In studying patients with unstable angina, Eisenberg et al. (24) found that

Table 3. Univariate Relations of Clinical Characteristics and Hemostatic Markers With Survival After Myocardial Infarction According to Cox Proportional Hazards Models

Variables	Hazard Ratio (95% CI)	p Value
Age (yrs)	1.03 (0.98–1.08)	0.20
Male	0.42 (0.16–1.07)	0.07
Hypertension	1.47 (0.58–3.72)	0.42
Diabetes	1.43 (0.51–3.97)	0.49
Smoking	0.40 (0.25–1.01)	0.06
Cholesterol (mg/dl)	0.99 (0.98–1.01)	0.32
Thrombolytic therapy	0.55 (0.20–1.53)	0.25
Revascularization	0.31 (0.07–1.37)	0.12
Anterior MI	1.47 (0.60–3.63)	0.99
Previous MI	0.68 (0.16–2.96)	0.61
Maximal CK (U/l)	1.00 (1.00–1.00)	0.97
Killip class IV	4.86 (1.55–15.19)	0.007
Left ventricular EF (%)	0.94 (0.90–0.99)	0.01
log (FPA)	1.54 (1.13–2.10)	0.006
log (F1+2)	2.03 (1.17–3.53)	0.01
log (TAT)	1.88 (1.27–2.79)	0.002

Abbreviations as in Table 2.

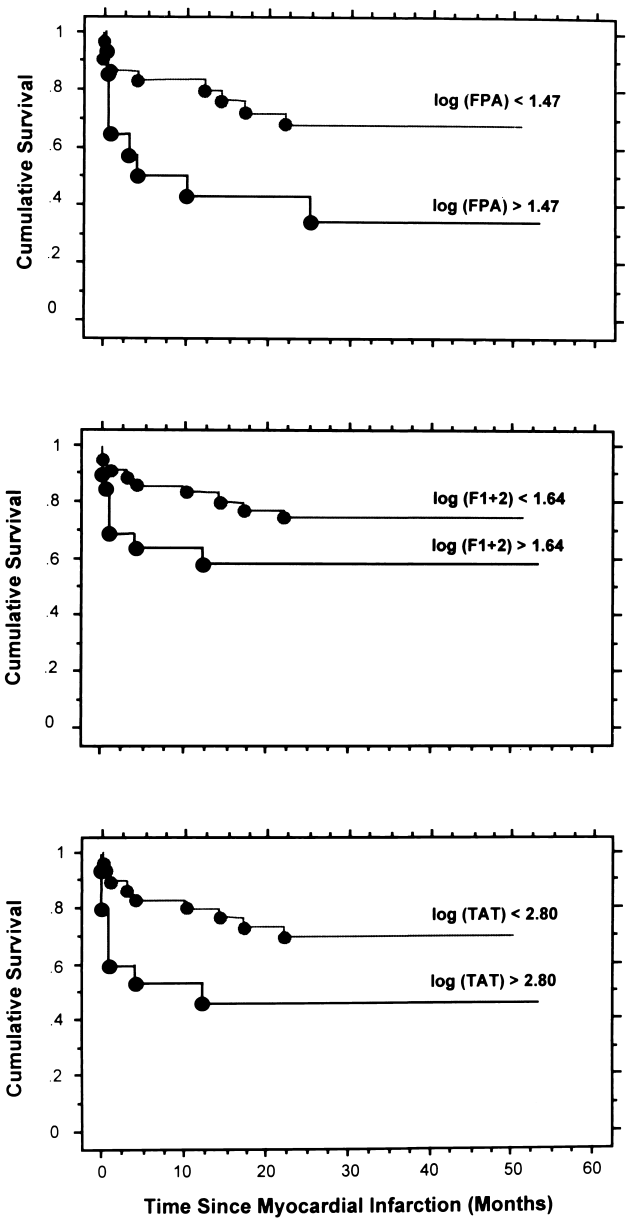

Figure 1. Kaplan-Meier curves of mortality under a dichotomy of hemostatic marker levels. The dichotomy was chosen to provide an equal number of deaths in the two comparison groups. **Top,** FPA; **middle,** F1+2; and **bottom,** TAT.

plasma concentrations of FPA were markedly elevated in 64% of patients with complex coronary lesions noted on angiographic examinations. This result demonstrated that increased thrombin activity indicated by increased concentrations of FPA might reflect the intrinsic procoagulant properties of the coronary atherosclerotic lesions. These kinds of complex coronary lesions may evoke recurrent ischemic events during the follow-up period and influence the prognosis of these patients. Another possible reason that increased hemostatic markers may affect prognosis is the duration of coagulation activation in patients with acute coronary syndromes. Merlini et al. (25) have shown that, in patients with unstable angina and myocardial infarction, plasma levels of F1+2 were elevated during the occurrence of the acute episodes and remained high even after 6 months of uneventful clinical course. It seems that, after the attack of acute coronary syndromes, there is a sustained hypercoagulability state in some patients. Hypercoagulability state creates a thrombogenic milieu, which may be related to the occurrence of subsequent thrombus formation with recurrent ischemic events. Thus, in the acute stage of myocardial infarction, increased hemostatic markers probably not only represent increased intracoronary thrombus formation but also mean more complicated and thrombogenic coronary lesions, and a more sustained hypercoagulable state. All these factors may influence the late prognosis.

Study limitations. One of the major limitations of this study is the relatively small number of enrolled patients. Previously reported poor prognostic indicators of myocardial infarction, such as diabetes mellitus, were found to be associated with poor survival in our study, but the increase in risk was not statistically significant. This association needs to be confirmed by further studies with larger numbers of patients. Nonetheless, the power of this study was large enough to detect the differences in the FPA level and the left ventricular ejection fraction between patients with and without cardiac death even in the multivariate analyses. Furthermore, we observed a relatively high mortality rate (30%) in our study population. Because our hospital is the major teaching hospital in the region, it becomes the final destination of referral for many severe patients. Therefore, our study cohort may not be representative of patients with acute myocardial infarction in the general population. However, selection bias, which occurs in a cohort study when knowledge of outcome (cardiac death in our study) is used in defining study groups (26), could not appear in our study because the clinical outcome was not known at the time of recruiting study participants. We did not assess the effects of drug treatment, including angiotensin-converting enzyme inhibitor and beta-blocker, on survival after myocardial infarction in this study. In fact, there were no differences between the participants with and without cardiac death in terms of the proportion of patients being given these drugs. Therefore, these medications should have no significant influences on the results of this study. Various revascularization procedures, including percutaneous transluminal coronary angioplasty and coronary graft bypass surgery, were used in patients with myocardial infarction in this study. They may affect the prognosis. Likewise, since there was also no significant difference in the proportion of patients receiving these procedures between the two groups of patients, these procedures could not have biased our study results.

Conclusions. In this study, we demonstrate that hemostatic markers measured in the early stage of acute myocardial infarction are correlated with subsequent cardiac mor-

tality in our patients, and the correlation of FPA with survival is independent of the residual left ventricular function after myocardial infarction. Because elevated hemostatic markers identify patients with myocardial infarction at increased risk of death, they have clinical potential to be used as prognostic indicators in risk stratification after acute myocardial infarction.

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